PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P045479PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NL2004/000551	International filing date *(day/month/year)* 04.08.2004	Priority date *(day/month/year)* 05.08.2003

International Patent Classification (IPC) or national classification and IPC
A61K47/34, A61K39/00

CORRECTED VERSION

Applicant
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1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.03.2005	18.10.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NL2004/000551

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-15	as originally filed
Claims, Numbers	
1-17	as originally filed
Drawings, Sheets	
1/3-3/3	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The following documents are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 (WO 01 34 801 A), disclosing the preparation of recombinant gelatines for vaccines and the vaccines obtained, also in dry form;
D2 (US 2003 064 074 A), disclosing the preparation of recombinant gelatines for vaccines;
D3 (Godard P et al, Journal of Polymer Science, 1978, vol. 16, no. 10, pages 1817-1828), disclosing the dependency of the gelation (crystallisation) and melting behaviour of aqueous gelatin on temperature, concentration and molecular composition;
D4 (Apostolov A. A. et al: Journal of Applied Polymer Science, (1999), 71(3), 465-470); disclosing the behaviour of water molecules in gelatin: crystallization behaviour and effects on gelation.

Unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

1. Novelty

The present set of claims 1-17 does not appear to be novel as required by Art. 33(1) and (2) PCT over D1. In fact, D1 discloses the advantages (in terms of immunogenicity and infection risks) of the use of recombinant/synthetic gelatines, also as mixtures of polymers with with different molecular weights, for the preparation of vaccine compositions with respect to the natural products. Moreover, although the limit of 2% water content is not mentioned, the vaccines are said to be obtainable also in dry (claim 18) or freeze-dried/lyophilized form which undergo primary and secondary drying. These forms are considerd to implicitely disclose a very low (<2%) water contents.
Analogous reasoning applies, mutatis mutandis, to D2.
In fact, the "measure" taken in order to prevent the composition of the present application to moisten in presence of athmospheric humidity appears to provide air and moisture tight

containers. Now these are also not explicitely disclosed, but this is the absolutely usual way of packaging especially injectables, since the skilled person would consider athmospheric humidity the main factor accelerating the deterioration of the products during their shelf life.
Therefore, D1 and D2 are novelty destroying for claims 1-17.

2. Inventive step

Even if claims 1-17 could be rendered novel by the restriction to a particular embodiment, their inventiveness according to Art. 33(1) and (3) PCT could not be acknowledged.
The problem is to provide a process which allows to obtain a particularly stable preparation. D1 and D2, which can be considered the closest prior art items, disclose the use of recombinant gelatin as a stabilizer for vaccine preparations. The difference in the present application is the mention of a very low water contents.
D1 and D2 themselves suggest the provision of a vaccine in "dry" form.
Moreover, in particular D3 shows that increasing water concentrations lower the temperature at which the physico-chemical properties of gelatin change (gelation/crystallization). The fact that in the present application the gelatin is recombinant and not natural (like in D3) should not affect this process, if the sequence of the recombinant protein mimics the native one.
It would therefore be obvious for the skilled person wanting to improve the vaccine shelf-life to reduce the water contents in the preparation as much as possible.

In addition, although e.g. a vaccine composition with less than 2% water content at least 3 months old has been claimed (claim 12), no data are provided in order to show that in fact the compositions maintain said low water concentration, nor that they have an improved long-term stability during their shelf life with respect to conventional gelatin formulations.